The enigma of prostatitis. Some historical perspectives on the pathogenesis of prostatitis

Dominic Prezioso[1], Kurt G. Naber[2], Bernard Lobel[3], Wolfgang Weidner[4], Feran Algaba[7], Louis J. Denis[5], Keith Griffiths[6]

[1]Clinica Urologica, University Federico II, Naples, Italy
[2]Department of Urology, Hospital St. Elisabeth, Straubing, Germany
[3]Department of Urology, Hospital Pontchaillou, Rennes, France
[4]Department of Urology, Justus-Liebig University, Giessen, Germany
[5]Oncology Centre Antwerp, Antwerp, Belgium
[6]International Prostate Health Council, Cardiff, UK
[7]Pathology Section, Fundació Puigvert, Autonomous University of Barcelona, Spain

Corresponding author:
Prof. Louis Denis MD
Oncology Centre Antwerp
Lange Gasthuisstraat 35-37
2000 Antwerp, Belgium
E-mail: louis.denis@skynet.be

Submitted: 7 March 2006
Accepted: 14 April 2006

Arch Med Sci 2006; 2, 4: 213-220

Abstract

Comparatively little research has been directed to the pathogenesis and treatment of prostatitis, an infectious, inflammatory disabling condition that can cause considerable pelvic pain, with a range of associated symptoms that can influence 50% of all men at some period in their life, often in their early adult years. This review considers the impact of prostatitis on patients and highlights the clear need for clinical research to enhance our understanding of the underlying biology of this ubiquitous disease. New insights into the molecular events that may be implicated in its pathogenesis suggest that more rational treatment options could well be developed, but throughout there is the recognition that prostatitis still remains an enigma.

Key words: prostatitis, inflammation, pathogenesis, prevention, treatment.

Historical perspectives on the pathogenesis of prostatitis

An effective approach to treatment demands a better insight into the diverse dysfunctional biological symptoms of prostatitis, including bacterial infection, lower urinary tract problems, severe pelvic pain, inflammation and sexual dysfunction. With regard to quality of life issues, prostatitis has been seen as equivalent to myocardial infarction, angina, or Crohn's disease, and is associated with anxiety, depression and impairment of intimate sexual relations, problems (Figure 1) not unusually leading to sexual dysfunction [1]. The major overriding facets of this multi-factorial disease encompass sexuality, cellular pathology, pathogens and the consequent inflammatory response of the prostate. A possible relationship with other dysfunctional prostate disorders, particular cancer, although controversial, does demand some thought.

Sexuality

Male sexuality has long been thought to have an overriding influence on prostate disease, although its precise nature remains blurred, possibly because of understandable difficulties in obtaining reliable data. Nevertheless, Rotkin

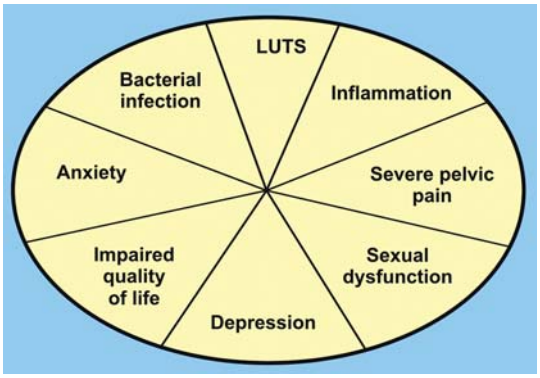

Figure 1. Symptoms and disease characteristics of CP/CPPS

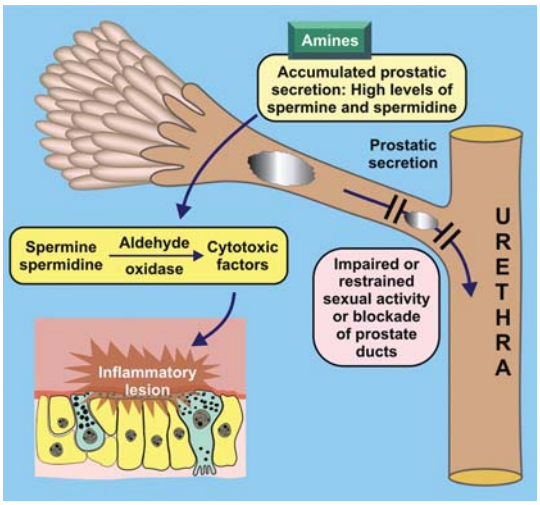

Figure 2. Diagrammatic representation of a possible influence of accumulated prostate secretory products on the development of an inflammatory response

[2, 3] firmly believed that sexual drive is related to the endocrine status of the male. He considered that sexuality influences the propensity to develop prostate disease and described a profile of "the man with such a propensity". Social class, occupation, education and income seem of little importance. At puberty, however, growth, dramatic endocrine changes and metabolic activity occur, together with an increasing awareness of gender differences and of females. A male becomes sexually motivated and masturbation and nocturnal emissions are common. A timid or shy personality may feel sexually repressed, possibly by restraints induced by moralistic issues, parents, religion, fear of admonition relating to the "consequences" of masturbation, such that he may not wish to seek coitus. Such restraints carried over post-pubertally, with coitus unfulfilled after induction, may induce an adverse response. Rotkin reported that patients with prostate cancer masturbated less and had less coital activity than control males.

Sexuality could relate to prostatitis by the very nature of the anatomy and function of the prostate, with duct blockage, or the accumulation of secretory products within the acini, due to limited sexual activity, inducing adverse events leading to inflammation (Figure 2). It seems reasonable to assume that the natural emission and ejaculation of such products is physiologically more efficacious than when it remains dormant within the ducts. In like manner, this relates to the reported [4, 5] effect of early first pregnancy on decreasing breast cancer risk in women, with milk flow allowing dormant duct fluid to be naturally removed. The concept suggests that "toxic products" in breast duct fluid [6] promote adverse cellular reactions, which can lead to breast pain, possibly cancer.

High intra-urethral pressure and a consequent reflux of urine into the prostate ducts has also been considered [7, 8] a contributing factor in the pathogenesis of prostatitis. Whether duct blockage or accumulation of secretory products can provoke an inflammatory response requires consideration, and certain older hypotheses [9] are worthy of note. The high concentration of aliphatic polyamines in prostate secretions is well documented and their adverse influence on DNA replication generally accepted. Williams-Ashman [10] hypothesised that "oxidation of spermine, or spermidine, by specific amine oxidases in prostate fluid, generated aldehydic products that were deleterious to the gland. Moreover, oxidases of the prostate microflora could equally have an adverse effect." Prostaglandins are important in the regulation of cell proliferation and in carcinogenesis, a role associated with polyamines. Polyamine synthesis is dependent on ornithine decarboxylase activity, which, in rat colonic epithelium, is considered prostaglandin-E2 dependent [11]. COX inhibitors restrain ornithine decarboxylase activity.

Understanding the pathology of prostatitis

The underlying pathology of "prostatitis" deserves more study, although routine prostate biopsy of patients presenting with the syndrome would be intrusive and painful. Nonetheless, cellular events associated with inflammation and epithelial cell disruption must be clarified. Paradoxically, areas of cellular proliferation are adjacent to inflammatory lesions, and tumour necrosis factor (TNF), intimately implicated in dysfunctional signal trafficking inducing epithelial atrophy and tissue necrosis (Figure 3), may contemporaneously provoke a compensatory cellular proliferation.

Some would believe [12, 13] that the inflammatory reaction, atrophy, tissue necrosis, epithelial cell disruption and associated hyperplasia could reflect early precancerous changes, an interesting but provocative concept. Prostatitis has never hitherto been remotely associated with cancer.

The contribution that Franks made to the pathology of prostate disease is considerable. Particularly interesting was our failure to appreciate his belief [14] that the prostate stromal elements exercised a major role in its growth regulatory events, being essential for epithelial proliferation. The close reciprocal interrelationship between stroma and epithelium is now fully accepted [15, 16].

In 1970, during a discussion [17] between Franks and McNeal, they outlined their views on cellular events relating to the origin of prostate cancer. McNeal considered that it developed from active glandular epithelium and prolonged "androgen stimulation", a statement which challenged Frank's belief that cancer arises from atrophic epithelium in an ageing prostate.

A delightful mutual respect governed these discussions as McNeal [18, 19], in introducing his concept of the zonal anatomy of the human prostate, described premalignant changes in hyperactive epithelium that supported a gradual, stepwise development of cancer. Franks disagreed, stating that a particular focal atrophy and post sclerotic hyperplasia is a precancerous lesion, being associated with lymphocytic infiltration and fibrosis of the periepithelial stroma, with areas of proliferation developing from atrophic epithelium. This pattern resembles small acinar carcinoma. McNeal stated that"the atrophy described is a type which is not secondary to ageing, but to an inflammatory process".

Whether these discussions impinge on the inflammatory response of prostatitis, or on the concept [10, 11] that proliferative inflammatory atrophy (PIA) constitutes a preneoplastic lesion, remain to be determined.

The natural history of prostate disease

Prostate cancer develops slowly as a heterogeneous cancer, over a period of 25-30 years (Figure 4), with initiation probably during the decade immediately following puberty, when early precancerous lesions, prostatic intraepithelial hyperplasia (PIN) and PIA may be identified. Interestingly, inappropriate intrauterine oestrogen-mediated gene imprinting can influence the prostate such that in later years a propensity to induce precancerous lesions is created. Genes associated with the IGF network and other oestradiol-related molecular processes would seem implicated, essentially a mechanism by which certain genes are"silenced" [20, 21]. Post-pubertal changes, epithelial hyperplasia associated with microscopic BPH [22] and with PIN [23], a lesion probably preceding micro-foci of latent cancer [24], occur in all men, worldwide, irrespective of race. The progression of latent to the malignant cancer phenotype is a feature of Western countries,

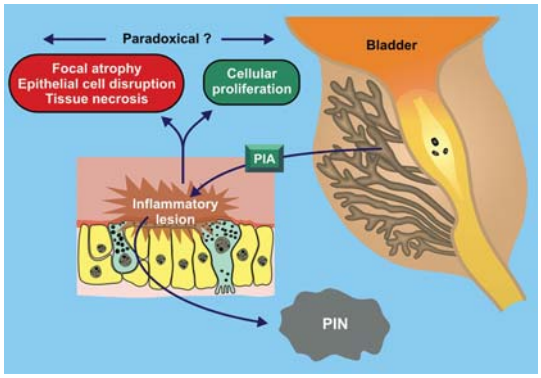

Figure 3. Focal cellular atrophy and proliferation associated with inflammation. Is proliferative inflammatory atrophy (PIA) an early stage in the development of PIN?

reflected in the geographical variation in prostate cancer incidence and mortality. Substantial evidence supports the concept that Asian dietary components may restrain this progression [19, 20], with interest centred on phyto-oestrogens such as genistein, an isoflavonoid constituent of soy protein, a staple of Eastern nutrition.

Imprinting: intrauterine oestrogenic signalling

Classical biology established that sexual differentiation, "maleness", was asserted by testosterone-directed events on the hypothalamus and the higher centres of the brain, during the first 24-48 hours of life [25, 26]. Testosterone organises the immature CNS to programme the induction of the behavioural aspects of maleness. Since the pituitary is not sexually differentiated, the signals programme the hypothalamus and higher centres such that male LH-RH secretory patterns are induced during puberty, and inappropriate neonatal exposure to oestrogens will therefore interfere with these events.

The concept that a transplacental transmission of an endocrine signal can promote cancer induction in later years was originally outlined by Herbst [27]. Inappropriate oestrogen-related imprinting can enhance the propensity for dysfunctional growth, preneoplasia and cancer in later life and a controversial issue centres on whether oestrogen-related imprinting relates to the cellular events that surround the induction of an inflammatory response within the prostate (Figure 3). Coffey [20] demonstrated that oestrogen imprinting promotes an inflammatory reaction in the rodent prostate, a spontaneous response induced in animals given a soy-free diet, but prevented by increasing soy-protein intake. PIA offers possibly a more rational insight into prostate cancer initiation during man's early adult life, this contemporary viewpoint of De Marzo, like that of Franks and McNeal earlier, emphasising that the

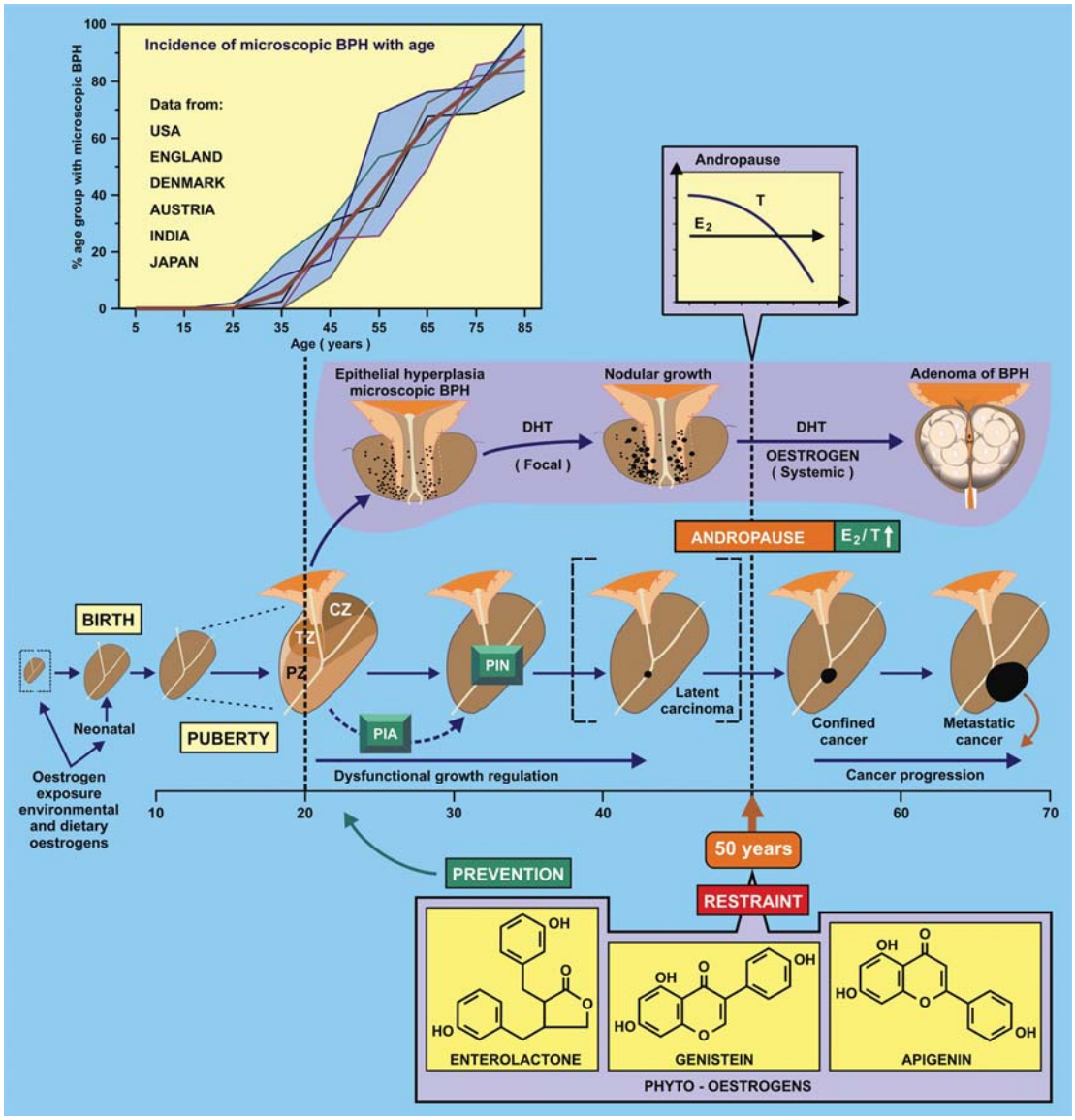

Figure 4. Portrayal of possible stages in the development of prostate disease

diffuse atrophy induced by androgen withdrawal is quite distinct from the focal atrophy related to inflammation, but which is also closely associated with cellular proliferation.

Free radicals, antioxidants and inflammation

That inflammation may relate to early cancer is not unreasonable, since an inflammatory response generates free radicals such as a highly reactive species of oxygen, which can be toxic and cause DNA damage [20, 28]. Macrophage and neutrophil infiltration to the lesion provides a source of oxygen radicals, which are normally removed by the superoxide dismutase enzyme system, the body's natural protective mechanism that transforms them into hydrogen peroxide (Figure 5). This is subsequently removed by glutathione-S-transferase-π (GSTπ) and glutathione peroxidases, catalysed by selenium.

Production of arachidonic acid from lipid membranes also generates reactive oxygen radicals, but is also converted by the cyclo-oxygenases (COX), to various eicosanoids, leukotrienes, prostacyclin, prostaglandin-E1 and -E2 and thromboxane A2, which encourage leukocyte infiltration into the inflammatory region and enhance pain receptor sensitivity.

NO, formed from the NO-synthase (NOS) enzyme system, plays a principal role in acute and chronic inflammatory processes, enhancing COX activity and proinflammatory prostaglandin production [29]. TNF, a cytokine produced by activated macrophages during infection, may also contribute to the inflammatory reaction of prostatitis [30], mediating both cell proliferation and apoptosis, although other cytokines, interleukin-1 (IL-1) and IL-8A, induce the

specific expression of a COX-2 isoform to exacerbate the process.

It is interesting, with regard to imprinting, isoflavonoids and rodent prostate inflammation [20], that ERβ signalling appears to influence glutathione-S-transferase activity [29], possibly explaining, in part, the potentially beneficial role of certain isoflavonoids such as genistein (Figure 5), mediated by ERβ [30]. Genistein and many of the ubiquitous dietary flavonoids, such as quercetin and apigenin, are effective anti-oxidants [21] that could influence GSTπ activity. Quercetin significantly improved the symptoms of patients with CPPS [31] and is reported to restrain the TNF-induced expression of IL-8. Coffey [20] has often stated that an inflammatory lesion is rarely seen in the human seminal vesicles, which contemporaneously rarely develop cancer. Moreover, GSTπ expression is upregulated in PIA, and also relevant is that gene silencing, the aberrant methylation of CpG islands of regulatory nucleotide sequences of the GSTπ gene, is the most prevalent somatic genomic change identified in prostate cancer. GSTπ methylation was identified in nearly 70% of PIN lesions and more than 90% of cancers [32], but in neither normal nor BPH prostate tissue, an epigenetic event possibly implicated in the transition from PIA to PIN (Figure 6).

Further reflections on prostatitis

Inflammation, prostaglandins and an overriding influence of reactive oxygen radicals seem at the very centre of the enigma of prostatitis, although neither bacterial infection nor oxidative stress are consistently identified in patients and, moreover, are found in asymptomaic men [33]. High WBC counts in prostatic fluid were found in 42% of asymptomatic men with an elevated serum PSA level [34]. Furthermore, only 5% of prostate biopsies from patients with symptoms of prostatitis have provided evidence of inflammation [35].

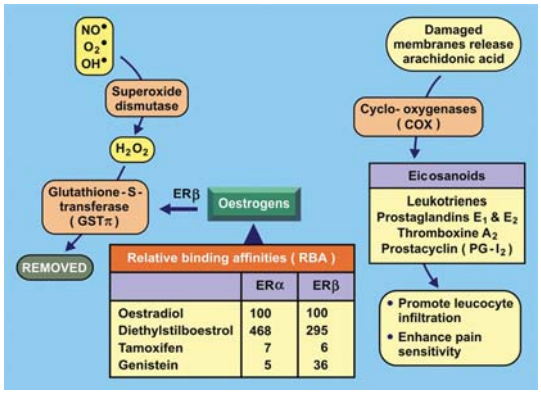

Figure 5. Natural defence mechanism against free radicals and the involvement of cyclo-oxygenases (COX enzymes) in the production of prostaglandins

Nonetheless, research is now focussed on the molecular events that underpin this enigmatic disease. NO and TNF assume leading roles, highlighting the therapeutic potential of NOS inhibitors. Various cells express inducible NO-synthase (iNOS), including macrophages and vascular smooth muscle cells, in response to the "inflammatory stimuli". A COX-1 constitutive isoform is present in the stomach and gut, where prostaglandins have a cytoprotective role. They may also be cytoprotective in cardiovascular cells. An inducible COX-2 isoform, expressed in response not only to cytokines but also to various growth factors, generates the large amounts of prostaglandins characteristic of an inflammatory lesion.

COX-2 expression would seem that of a primary response gene, akin to c-fos and c-jun, activated as part of the AP-1 mitogenic signalling network [36]. Anti-inflammatory steroids such as glucocorticoids and the growth inhibitory factor TGF-β inhibit TNF release and thereby the expression of iNOS and COX-2. COX-enzymes are encoded by independent genes [37] and controversy now centres on the clinical efficacy of anti-inflammatory drugs and specific COX-2 inhibitors in reducing the effects of COX-2 but sustaining the cytoprotective action of COX-1.

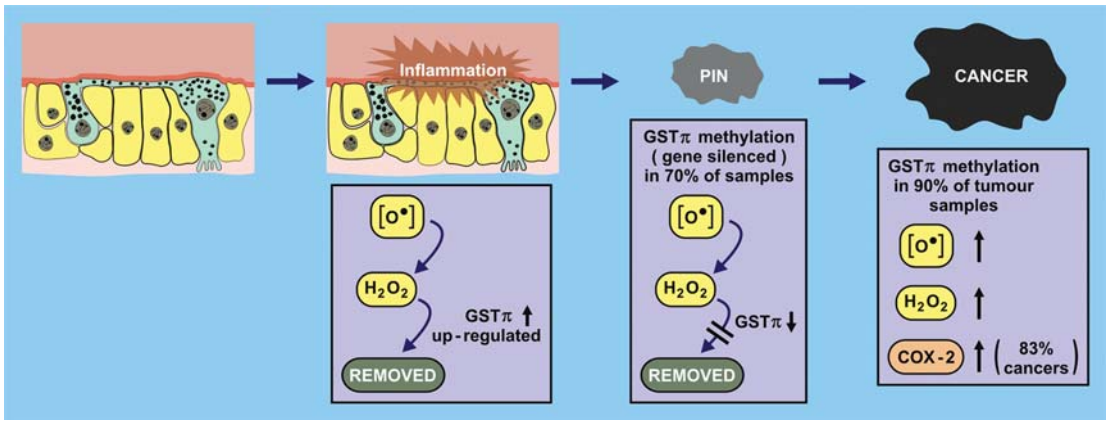

Figure 6. Some relevant molecular changes possibly related to the development of PIN

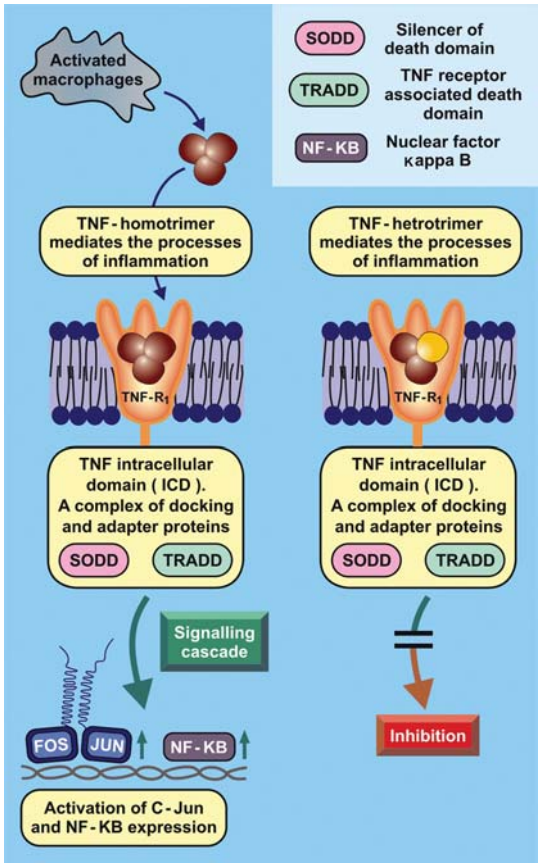

Figure 7. Potential blocking of TNF-signalling mechanisms

Inappropriate TNF signalling is implicated not only in prostatitis, but also in rheumatoid arthritis and inflammatory bowel disease, and new drugs that restrain TNF-signalling offer an approach to treatment. TNF associates with its receptor as a homotrimer [38], and variant TNF molecules have been designed, with one of the three TNF molecules modified [39] such that on clinical administration the resultant heterotrimer blocks the normal activation of the native TNF-receptor complex (Figure 7).

The paradoxical molecular events that promote both cellular proliferation and cell death, as well as tissue necrosis, particular features of prostate inflammation, are those triggered by TNF-signalling pathways. TNF-mediated signalling activates two important transcription factors, nuclear factor kappaB (NF-κB) and c-Jun, their complex crosstalk implicated not only in the inflammatory response but also in cell proliferation and cell death.

The signalling networks governing prostate inflammation are being unravelled and whereas to date the presence of white blood cells offers a simple marker of an inflammatory reaction, levels of proinflammatory cytokines will soon provide parameters by which to manage CPPS. Already, TNF and IL-1β have been identified in prostate fluid and semen [38, 39], with higher levels in patients with IIIA disease, relative to IIIB. Higher levels of ENA-78 and IL-8 in prostate fluid were found in patients with more than 10 WBCs in the fluid than in those with less [40]. Such analysis could be a prerequisite to the initiation of anti-inflammatory therapy, rather than the empirical approach on the basis of their analgesic effect.

Any suggestion of a relationship between prostate inflammation and preneoplasia will invoke controversy. Can PIA progress to PIN? Cancer cells certainly generate large amounts of hydrogen peroxide [41] and EGF stimulates its production in vascular smooth muscle [42], triggering MAPK signalling and cell replication, a response blocked by anti-oxidants. Interestingly, PSA also increases hydrogen peroxide levels in prostate cancer cells [43]. Elevated levels of Nox1 and hydrogen peroxide are found in prostate cancer [44] and Nox1, a superoxide generator, has been implicated in cell transformation [45]. Nox1 triggers angiogenesis, and transfected into DU145 prostate cancer cells increases hydrogen peroxide generation and tumourgenicity [46].

Enhanced production of reactive oxygen radicals, of hydrogen peroxide, prostaglandins and COX-2, would seem to be a feature of prostate cancer, which has the highest expression of COX-2 mRNA of all human tissues [47] and elevated levels of prostaglandins [48, 49], promoting metastatic potential. COX-2 is over-expressed in more than 80% of human prostate cancers [50]. The complexity of the MAPK signalling network does little but confound, integrating messages from a range of extracellular stimuli. Whatever the outcome, the dissection of the molecular events implicated in prostatitis will be of great interest.

There are other perspectives

Prostate inflammation can also be incited by physical injury, or trauma to the pelvic region. It would seemingly be a consequence of inappropriate oestrogen imprinting, not only by natural oestrogens, but the ubiquitous array of environmental oestrogens so prevalent in modern life. Oestrogens may influence mediators of inflammation such as IL-1β and IL-8, the expression of which they down-regulate [51]. It is noteworthy that Mepartricin (Ipertrofan: SPA, Società Prodotti Antibiotici SpA, Milan), which irreversibly binds gut oestrogens [53] to interfere with their re-absorption through the enterohepatic circulation, thereby decreasing plasma oestrogen levels, has been effectively used in the clinical management of category III CPPS [54].

Dysfunctional innervation of the lower pelvis, refluxing of urine into the prostatic ducts, or a relative lack of sexual activity that allow prostate secretory

products to provoke adverse reactions, or harbouring of pathogens, are some of the factors that may have a role in the pathogenesis of prostatitis. Sexual dysfunction, depression and anxiety may be fostered by a dysfunctional pelvic sympathetic or parasympathetic network, which induces lower urinary tract symptoms, so often identified with prostatitis. Symptomatic consequences are pelvic floor muscle tenderness, myofascial trigger points and sphincter hyperactivity [33].

Again, considering historical perspectives, toxic products within prostate secretions and their deleterious effects were a feature of conferences of yester-year, directed to the adverse influences of environmental factors. The report [55] that oestrogens enhanced the sensitivity of prostate explants to methylcholanthrene, which induced epithelial hyperplasia, was fascinating. Another contentious issue centred on the higher incidence of prostate disease in men in the heavy metal industry and the influence cadmium might have on intra-prostatic zinc metabolism. Cadmium can be present in relatively high concentrations in urine, and although its principal adverse effect is directed to the vasculature of the testis [56] it does localise in the nucleoli and lysosomes of prostate epithelial cells. Electron microscope microanalysis [57-59] suggested that cadmium uptake enhanced basal cell activity, also recognised after castration. Studies of the rat prostate lateral lobe show that cadmium uptake causes local necrosis and subsequent basal cell proliferation. Possibly in context is the suggestion [60] that metal-invoked site-specific DNA damage, associated with high levels of hydrogen peroxide, may be implicated in dysfunctional growth regulation.

The enigma of prostatitis persists, but now controlled clinical studies and the exciting input from molecular biology will do much to increase our understanding of this most complex syndrome and provide a basis for the development of new approaches to treatment and management. "A great deal has already been achieved, but so much more remains to be done."

Acknowledgements

The authors would like to thank Mr. David Griffiths for his kind permission in allowing them to use the illustrations presented in this paper and in the paper in the June issue. Mr Griffiths created and owns the copyright of the illustrations (CompGraphics Services, Cardiff, UK. – email: DGcompgraphics@aol.com).

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